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Medical Frontiers:
Confronting Alzheimer's

Promising Vaccine Targets Ravager of Minds

By Susan Okie

Washington Post Staff Writer

Tuesday, May 8, 2001; Page A01

TAMPA -- The moment he hits the cool water of the laboratory's baby pool, the brown mouse swims for dear life. He is 17 months old -- elderly for a mouse -- but he seems to have his goal in mind. He paddles to the center of the daisy-shaped water maze, looks around, then heads rapidly down the correct aisle and clambers to safety on an invisible platform.

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An aging mouse's successful navigation of a maze might seem unconnected to the plight of the estimated 4 million Americans who have Alzheimer's disease, a common and incurable brain disorder that steals its victims' memories and personality. But maze-swimming mice here are testing a remarkable vaccine that one day may reduce or prevent brain damage from Alzheimer's, which is predicted to become epidemic as the nation's elderly population grows.

Mice at the University of South Florida have been given mutated human genes that produce age-related brain degeneration much like Alzheimer's disease. To the astonishment of scientists conducting the studies, vaccinating these mice during mid-life slowed progression of their brain disorder and preserved their ability to learn.

The vaccine, developed by California scientists with Elan Corp. of Dublin, Ireland, and now undergoing safety testing in people, is one of several promising new approaches being pursued for Alzheimer's disease, a disorder whose current treatments produce only partial and short-lived improvement. In a field where progress has been glacially slow for many years, scientists now speak of intense competition and rapidly emerging discoveries.

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"We tried about a dozen things that didn't work and now everything we're trying is working," said Dave Morgan, a neuroscientist at the University of South Florida who is testing the vaccine and other experimental treatments in transgenic mice. "I'm very encouraged."

The upsurge in innovative research stems in part from a clearer understanding of precisely what goes wrong in the brains of people with the disease. For example, researchers have identified two key enzymes that produce beta-amyloid, a waste protein that builds up in the brains of Alzheimer's victims and appears to be central to the destructive process. Several major drug companies are racing to identify and develop enzyme-blocking drugs called secretase inhibitors that they hope will reduce beta-amyloid accumulation. At least one company, Bristol-Myers Squibb Co., has begun testing such a drug in patients.

In addition, researchers are evaluating an array of compounds -- ranging from anti-inflammatory drugs, estrogen and cholesterol-lowering agents to various vitamins and supplements -- to see whether they can prevent Alzheimer's or delay its onset. Last month, in the first test of gene therapy for the disease, doctors in California implanted skin cells engineered to produce nerve growth factor into the brain of a woman with the disorder.

However, it may turn out that to stave off Alzheimer's disease, people will have to begin treatments such as the vaccine or enzyme-blockers in late middle age, perhaps a decade or two before symptoms would be expected to appear. At present, no medical test can predict who will develop the illness. Researchers say that if effective

preventive treatments become available, such a test will be urgently needed.

A Stealthy Assault

Like AIDS, Alzheimer's is an ultimately fatal disorder that begins its stealthy assault years before problems with memory or learning make its presence apparent.

"The baby boomers are the people now getting Alzheimer's disease," said Trey Sunderland, chief of geriatric psychiatry at the National Institute of Mental Health (NIMH). "They just don't know it."

The biggest risk factor for Alzheimer's disease is growing old. The disorder is rare in people younger than 60, but its frequency doubles every five years after 65. By age 80, about 9 percent of people have the condition; by age 90, the prevalence is 29 percent. In the next half-century, as the elderly population grows, the number of Americans with Alzheimer's disease will roughly

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quadruple. The total, estimated at between 2 million and 4 million now, is projected to be as high as 14 million by 2050.

The earliest sign that something is amiss in the brain is usually loss of recent memory. Later, people with the disease develop poor judgment, confusion and personality changes. They lose the ability to care for themselves and may fail to recognize their loved ones. Most live for an average of five to nine years with the illness, eventually becoming bedridden and dying of pneumonia or other infections.

Dorothy Ordway's husband and daughters first realized that she had Alzheimer's disease about six years ago, when the family rented a vacation house and Ordway kept forgetting where her bedroom was. A former banker, she was also neglecting to pay her bills.

For several years, Ordway, 80, attended a senior day care center and continued to live in her Parkville, Md., home, but she grew increasingly confused.

"She thought I was her father," recalled her husband, Thomas, 85. Last summer, after she began leaving the stove on, her family was forced to move her to an assisted-living facility.

"She knows that she's not home, but she doesn't know where she is," said her daughter, Nancy Barlow. "The day before yesterday, I'm not sure she could have told you what my name was . . . I really sensed for the first time that she wasn't quite sure."

For the family, Barlow added, watching her mother's decline "is a grieving process."

Under a microscope, the brain of someone who has died of Alzheimer's disease resembles a junkyard. Scattered among the surviving nerve cells of the cerebral cortex -- the cells responsible for thoughts, learning and decisions -- are myriad clumps or "plaques" of beta-amyloid, a waste protein toxic to nerve cells that is a hallmark of the illness. Around the plaques cluster disease-fighting cells that seem to be trying unsuccessfully to clean up or wall off the mess. Everywhere are misshapen pieces of dead nerve cells, their insides choked with tangles made of a twisted, cable-like protein called tau.

"Nerves die and all you have left are the tangles," said pathologist Juan C. Troncoso of Johns Hopkins School of Medicine as he examined such a brain. "What we're not seeing here is perhaps what is most important." The tissue specimen showed few synapses, the connections between nerve cells through which they communicate. A healthy brain cell typically has as many as 15,000 synapses with other cells. "These individuals have a tremendous amount of synaptic loss," Troncoso said.

The Vaccine Inspiration

Faced with such wreckage, researchers have tried for years to determine what

sets off the destruction -- and in particular, whether amyloid plaques or tau tangles are the primary trigger. Although both appear to contribute, experts said there is now convincing evidence that buildup of beta-amyloid is at the root of the disease.

Key to this conclusion was the discovery of three human genes that, when mutated, have been found to cause inherited Alzheimer's in rare families. All three genes are involved in making beta-amyloid. One contains the code for a larger protein that is snipped apart to produce the toxic fragment; the other two carry instructions for an enzyme that does some of the snipping.

"Every known mutation ultimately increases" buildup of beta-amyloid, Morgan said.

Once these genes were identified, scientists began introducing mutated versions into the fertilized eggs of mice, hoping to engineer a mouse strain that would develop something similar to Alzheimer's disease. By the mid-1990s, scientists at Elan's laboratories in South San Francisco had such a strain and wanted to devise experiments that might lead to diagnostic tests or treatments.

At that point, biochemist Dale Schenk had an idea that he calls "a little bit crazy." Why not try vaccinating the mice against beta-amyloid?

Schenk reasoned that the protein accumulated in the brain because it was being produced faster than it was removed. He thought that if he could stimulate the immune system to make antibodies, proteins that would stick to beta-amyloid and tag it as an unwanted substance, they might shift that balance, perhaps reducing or preventing the buildup.

The idea was revolutionary because most Alzheimer's experts believe that the inflammation provoked by amyloid plaques contributes to destruction of brain cells. Many predicted that stirring up the immune system with a vaccine would only make the disease worse.

"It was breaking a lot of paradigms," Schenk acknowledged. "I had a lot of arguments with my colleagues. . . . This experiment ended up at the absolute bottom of the priority list of things to do."

Schenk first vaccinated six-week-old transgenic mice and found that the vaccine completely protected them from developing amyloid plaques. Even when the vaccine was given to older animals that already had plaques in their brains, it reduced the appearance of additional plaques and seemed to make some of the existing beta-amyloid deposits disappear. Under the microscope, it appeared that microglial cells -- wandering brain cells that clean up debris and fight infection -- were becoming activated by the vaccine and gobbling up the plaques.

"That was a major surprise," Schenk recalled.

Schenk's 1999 paper on the Elan vaccine created a sensation, not least because

the unexpected findings suggested that vaccines might be helpful in disorders where no one had thought of using them. His results have since been confirmed by other researchers.

But no one knew whether the treatment could improve learning or memory in affected animals. Without such evidence, medical researchers would be reluctant to try it in people. "You may remove the amyloid, but patients may not do any better," noted Hopkins' Troncoso.

Using the Florida transgenic mice, Morgan and his team tried to address that question. They used a water maze shaped like a daisy with six petals to test animals' "working memory": the ability to learn and remember new information, which is the earliest brain function affected by Alzheimer's.

Each day, the escape platform is placed at the end of a different arm of the maze. A mouse must swim until it locates the platform, which is invisible from the surface. Mice in the experiment were given five trials each day, testing their ability to learn and recall the platform's location. The next day, the platform was moved to a new location.

"It's like you have to remember where you parked your car," said David Diamond, a behavioral neuroscientist who designed the water maze used in the study.

Morgan and his colleagues gave transgenic animals monthly injections of a vaccine similar to the one developed by Elan, starting at seven months of age. He first tested them in the maze when they were 11 months old, expecting that brain inflammation caused by the vaccine would worsen their performance. Instead, they learned the maze as fast as normal mice. "We were completely wrong," he said. "They were just dynamite."

By 15 months of age, transgenic mice that had not gotten the vaccine had developed severe brain disease and could no longer navigate the maze. But the vaccine recipients could still learn and remember the platform's location, although they took longer to master it than normal animals. Morgan and his team are now studying whether the vaccine still protects the brain when the treatment is begun later in the animals' lives.

Testing in Humans

The Florida team's promising findings and those of another group in Canada have spurred Elan's efforts to test the vaccine in Alzheimer's patients. Last year, a small safety study in this country found no significant side effects. The vaccine is now undergoing a multidose safety trial involving about 80 patients in Great Britain who have mild or moderate Alzheimer's disease. The results are expected within the next two months. If they are favorable, the company hopes to begin testing the vaccine in a larger number of patients to see whether it has a favorable impact on their illness.

"I think it provides some hope," said Schenk, who is to receive a prize for his discovery today at the American Academy of Neurology's annual meeting.

Many researchers are nervous about the prospect of giving a vaccine to activate the immune system in the brain, reasoning that if it triggers inflammation or other adverse effects, doctors won't be able to turn off the process. Some have suggested it might be safer simply to give patients periodic injections of antibodies against beta-amyloid -- much as gamma globulin shots were once given to prevent hepatitis -- because the treatment could be stopped if side effects developed.

The NIMH's Sunderland, who is trying to develop a predictive test for Alzheimer's disease, is studying a group of healthy volunteers who are at higher-than-average risk because they have parents or siblings with the disorder.

"They ask, 'Should I get the vaccine?'" Sunderland said. "My opinion is, 'No. Not now.' "

Nevertheless, Sunderland said he is encouraged by the results so far. He said he suspects that an Alzheimer's vaccine may work better for preventing the disease than for treating it once the brain has become severely affected.

"Let's say they give it to Alzheimer's patients and it fails," he said. "It might seem a devastating blow to the vaccine concept, but maybe they gave it to the wrong people. Right now, there is no flashlight . . . telling you where to point your treatment, and when."

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